

The effect of empagliflozin on monocyte high-density lipoprotein ratio in patients with type 2 diabetes mellitus

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ABSTRACT

Aim: We aimed to investigate the effect of empagliflozin, which is started in patients with type 2 diabetes mellitus (T2DM), on neutrophil lymphocyte ratio (NLR) and monocyte high-density lipoprotein ratio (MHR), which are used as inflammation, glycemic control and oxidative markers.

Material and Method: The file systems of T2DM patients who used empagliflozin for at least 12 weeks were retrospectively analyzed. Demographic data of the patients were recorded. biochemical and hemogram parameters were compared before and after empagliflozin.

Results: 194 patients were included in the study. Plasma fasting glucose ($p<0.001$), hemoglobin A1c (HbA1c) ($p<0.001$), low-density lipoprotein cholesterol (LDL-C) ($p=0.041$), NLR ($p=0.002$) and MHR ($p=0.042$) values of T2DM patients after empagliflozin treatment were statistically significantly decreased compared to pre-treatment with empagliflozin. HDL-C value ($p=0.003$), on the other hand, increased significantly after empagliflozin.

Conclusion: NLR and MHR are inexpensive and practical markers of inflammation. This result shows us that NLR and MHR should be used as inflammation markers in patients using empagliflozin.

Keywords: Empagliflozin, MHR, NLR

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease with a complex pathophysiology. Increasing insulin resistance, progressive deterioration of β -cell function, dysfunctional adipocytes, gastrointestinal incretin defects, increased glucose reabsorption from the kidneys, hyperglucagonemia, and neurotransmitter dysfunction may contribute to development of diabetes. Glucose control is a central focus in the management of T2DM, and reducing hyperglycemia has been shown to decrease microvascular complications of diabetes (1). Chronic inflammation plays an important role in the pathogenesis of diabetes, its development and complications (2,3). Studies show that the levels of inflammatory cytokines such as CRP, IL-1, IL-6, TNF- α increase in patients with diabetes (4). Neutrophil/lymphocyte ratio (NLR) is an indicator of systemic inflammation and is accepted as a marker of inflammation in complications such as microvascular and macrovascular in diabetic patients (5). The monocyte-to-high density lipoprotein ratio (MHR) has recently been implemented as an indicator of inflammation and oxidative

stress. MHR indicates inflammation and oxidative stress due to the proinflammatory effect of the monocytes, as well as the anti-inflammatory and antioxidant effect of the high-density lipoprotein cholesterol (HDL-C). Several studies have used these metrics to determine whether inflammation and atherosclerosis contribute to the etiopathogenesis of cardiovascular and cerebrovascular diseases. MHR has been found to be significant as a biomarker in the development of microvascular complications in diabetic patients (6,7). Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, is a newly developed oral antidiabetic drug to enhance renal glucose excretion or glycosuria and reduce hyperglycaemia in an insulin-independent manner by highly selective inhibition of SGLT2. SGLT2 is mainly located in the apical brush border membrane of the S1 segment of the proximal convoluted tubules, which regulates 90% of the reabsorption of glucose from glomerular filtrate. Therefore, SGLT2 inhibitor can increase the urinary glucose level and reduce blood glucose. Empagliflozin is different from conventional antidiabetic drugs, which

rely on insulin secretion, and represents a novel class of antidiabetic drugs. It has been approved for the treatment of type 2 diabetes in adults since 2014 (8,9). In our study, we aimed to investigate the effect of empagliflozin, which is started in patients with Type 2DM, on NLR and MHR, which are used as inflammation, glycemic control and oxidative markers.

MATERIAL AND METHOD

This study was planned retrospectively. The study was carried out with the permission of Hitit University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 29.12.2021, Decision No: 2021-88). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who applied to our internal medicine outpatient clinic between 01.01.2019 and 01.01.2022 with a diagnosis of T2DM, who were started on empagliflozin 10 mg and used for at least 12 weeks were screened. 194 patients who met the inclusion criteria were included in the study. Inclusion criteria for the study; Patients who have not used empagliflozin before and have received empagliflozin treatment for at least 12 weeks, patients over the age of 18, patients under 75 years of age, patients who are not pregnant, those without acute infection, those who have not started antihyperlipidemia treatment in the last month and have not changed, and those who do not use drugs affecting the bone marrow, spleen-related disease, acute and chronic inflammatory disease and consists of people without a history of malignancy. Exclusion criteria; Type-1 DM, who use empagliflozin for less than 12 weeks, pregnant women and patients with chronic renal failure. Demographic data, comorbidities and diabetes medication used before empagliflozin were noted. Glucose, hemoglobin A1c (HbA1c), HDL-C, low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and hemogram parameters were recorded before and after empagliflozin.

This study was approved by the university/local human research ethics committee, and all procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

Statistical Analysis

IBM SPSS 22 program was used for data analysis and statistical analysis. Student's T test was used for intergroup comparisons of normally distributed parameters as well as descriptive statistical methods

(mean, standard deviation, ratio) when evaluating study data; Mann-Whitney U test was used for the intergroup comparisons of non-normally distributed parameters. In addition, Wilcoxon Signed Rank test was used. The results were evaluated at the 95% confidence interval and the significance level of $p < 0.05$.

RESULTS

A total of 194 patients, 86 male and 108 female, using empagliflozin were included in our study. The mean age was 63.12 ± 4.12 in men and 64.26 ± 5.90 in women. The duration of DM was 13.05 ± 5.34 in men and 14.09 ± 6.01 in women. DM drugs used before empagliflozin, comorbidities and complications of DM are shown in **Table 1**.

Table 1. Demographic and clinical data of the patients	
Sex=n (%)	
Male	86 (44.3)
Female	108 (55.6)
Age (years)±SD	
Male	63.12 ± 4.12
Female	64.26 ± 5.90
Disease duration (years) ± SD	
Male	13.05 ± 5.34
Female	14.09 ± 6.01
Comorbidity (n)	
Hypertension	105
Hyperlipidemia	47
Coronary artery disease	31
Cerebrovascular disease	7
None	64
DM medication before empagliflozin(n)	
Insulin	75
Metformin	49
Linagliptin	24
Vildagliptin	28
Pioglitazone	27
Other	10
DM microvascular complications(n)	
None	94
Neuropathy	39
Nephropathy	29
Retinopathy	32

Plasma fasting glucose, HbA1c, LDL-C, NLR and MHR values of T2DM patients after empagliflozin treatment were statistically significantly decreased compared to pre-treatment with empagliflozin ($p < 0.05$). HDL-C value, on the other hand, increased significantly after empagliflozin ($p < 0.05$) (**Table 2**).

There was no statistically significant difference in blood parameters of T2DM patients with neuropathy after using empagliflozin ($p > 0.05$) (**Table 3**).

Table 2. Comparison of biochemical and hemogram parameters of T2DM patients before and after empagliflozin			
	Before Empagliflozin Mean±SD	After Empagliflozin Mean±SD	p
Plasma fasting glucose (mg/dL)	188.02±63.80	146.69±57.04	<0.001*
HbA1c (%)	8.24±1.83	6.37±1.43	<0.001*
Triglyceride (mg/dl)	208.51±72.28	192.60±60.17	0.063
Total Cholesterol (mg/dl)	173.66±52.73	171.72±49.24	0.071
HDL-C (mg/dl)	41.82±11.83	46.64±13.61	0.003*
LDL-C(mg/dl)	108.91±37.27	101.87±43.28	0.041*
ALT (IU/L)	23.19±11.41	24.18±13.06	0.073
AST (IU/L)	20.93±6.93	21.22±9.54	0.967
White blood cell	8.55±4.64	8.40±3.48	0.816
Hemoglobin (g/dl)	13.08±4.07	13.87±2.27	0.163
Neutrophil(10 ³ /mm ³)	5.01±1.38	4.93±1.19	0.263
Lymphocyte (10 ³ /mm ³)	2.62±0.43	2.67±0.58	0.107
Monocyte (10 ³ /mm ³)	0.49±0.11	0.50±0.73	0.473
NLR	1.92±0.63	1.74±0.78	0.002*
MHR	0.01171±0.00401	0.01072±0.00941	0.042*
Platelet (10 ³ /mm ³)	298.76±72.34	287.09±71.23	0.118
*p<0.05, SD: standard deviation			

Table 3. Comparison of biochemical and hemogram parameters of T2DM patients with diabetic neuropathy before and after empagliflozin			
	Before Empagliflozin Mean±SD	After Empagliflozin Mean±SD	p
Plasma fasting glucose (mg/dL)	196.96±54.82	183.69±47.03	0.634
HbA1c (%)	10.04±1.97	9.61±1.23	0.072
Triglyceride (mg/dl)	188.71±62.38	184.59±61.24	0.963
Total Cholesterol (mg/dl)	182.31±46.28	171.81±47.28	0.821
HDL-C (mg/dl)	40.36±10.47	43.75±11.58	0.053
LDL-C (mg/dl)	107.99±34.53	108.78±36.41	0.061
NLR	3.69±0.99	3.36±0.78	0.072
MHR	0.01611±0.00321	0.01539±0.00611	0.143
SD: standard deviation			

DISCUSSION

In our study, after empagliflozin treatment in T2DM patients, plasma fasting glucose, HbA1c, LDL-C, NLR and MHR values decreased significantly, while HDL-C values increased significantly. The prevalence of type 2 diabetes mellitus has doubled over the past 3 decades and is likely to affect a half a billion people in the next 3 decades (10). Female gender and advanced age are predisposing factors for T2DM (11). Of the patients participating in our study, 55.6% were female and 44.3% were male. The mean age was found to be 64.01 years.

Sodium glucose cotransporter 2 (SGLT2) inhibitors have a unique mechanism of action leading to excretion of glucose in the urine and subsequent lowering of plasma glucose. This mechanism is independent of β -cell function; thus, these agents are effective treatment for type 2 diabetes mellitus (T2DM) at theoretically any disease stage. Empagliflozin is one of three approved SGLT2 inhibitors (12). In a study by Rosenstock et al. (13) a statistically significant decrease was found in HbA1c, fasting plasma glucose and body weight after 12 weeks of empagliflozin treatment. In our study, similar to the

literature, a statistically significant decrease was found in the fasting plasma glucose and HbA1c averages of the patients after empagliflozin ($p<0.001$).

SGLT2 inhibitors reduce body weight and visceral adiposity, and improve various metabolic abnormalities associated with metabolic syndrome such as blood pressure, lipid profile, and serum uric acid level (14). SGLT2 inhibitors are associated with a small increase in HDL-C as well as an increase in LDL-C with concomitant reductions in triglyceride levels (15,16). In addition, a meta-analysis of 34 randomized controlled trials showed that the administration of SGLT2 inhibitors increased HDL-C (mean difference 1.93 mg/dL), LDL-C (mean difference 3.5 mg/dL) and decreased serum triglycerides (mean difference 7.8 mg/dL) (17). In the comparison study of empagliflozin 10mg, empagliflozin 25mg and placebo by Hach et al. (18) small increases in HDL-cholesterol and LDL-cholesterol and a small decrease in triglyceride levels were observed in the empagliflozin group. In our results, there was a significant increase in HDL-C and a significant decrease in LDL-C (HDL-C $p:0.003$, LDL-C $p:0.041$), while the decrease in triglyceride level was not

statistically significant ($p:0.063$). In a retrospective study by Yuya et al. (19) in non-alcoholic fatty liver patients, patients using dipeptidyl peptidase-4 inhibitor and SGLT2 inhibitor for 24 weeks were analyzed. Decreases in transaminase activities were found to be similar in both groups. We did not detect any significant changes in AST and ALT values before and after empagliflozin.

MHR and NLR values are used as markers of inflammation in diabetic patients (20,21). There are studies showing the anti-inflammatory and antioxidant properties of empagliflozin treatment in T2DM patients (22,23). However, we could not find any study in the literature investigating the effect of empagliflozin treatment on MHR and NLR levels. Chronic inflammatory disorders and dyslipidemia in type 2 diabetes mellitus (T2DM) are essential contributors to the development of atherosclerotic cardiovascular disease. High NLR and MHR values are associated with cardiovascular disease in T2DM patients (24,25). Cardiovascular mortality is the principal cause of death in individuals with T2DM. The recently published Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study demonstrated that in T2DM patients with high cardiovascular disease risk empagliflozin reduced the primary major adverse cardiac event end point (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) by 14% (26). In our study, a significant decrease was found in NLR and MHR values after empagliflozin (NLR $p:0.002$, MHR $p:0.042$).

Up to 50% of diabetes patients suffer from microvascular complications, including diabetic peripheral neuropathy, diabetic retinopathy and diabetic kidney disease (27,28). There are also evidences that inflammation may play a key role in occurrence of microvascular complications. This result shows us that NLR and MHR should be used as inflammation markers in patients using empagliflozin. (24,29,30). In addition, oxidative stress plays a strong role in the pathogenesis of diabetic complications (31). In the study of the effect of empagliflozin on diabetic microvascular complications, Eid et al. (32) did not find any effect on neuropathy in T2DM subjects. In the study of Mehta et al. (33) patients using empagliflozin did not detect any difference in the improvement of diabetic neuropathy when compared to patients using other oral antihyperglycemic drugs. In our study, we did not find any changes in the biochemical and hemogram parameters of diabetic neuropathy patients using empagliflozin in accordance with the literature.

CONCLUSION

Empagliflozin's decrease in NLR and MHR in type 2 DM patients shows that it provides anti-inflammatory activity in these patients

Limitation

This study has some limitations.

1. It is not known that the patients took antidiabetic drugs regularly before empagliflozin
2. Whether the drug use is regular after empagliflozin treatment
3. Failure to evaluate diabetic neuropathic complaints and findings after empagliflozin

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Medical Faculty Non-interventional Clinical Researchs Ethics Committee (Date: 29.12.2021, Decision No: 2021-88).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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